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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/459,141	06/02/1995	PHILLIP W. BERMAN	P0233C6	3929

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	

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37

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/459,141	Applicant(s) BERMAN ET AL.	
	Examiner Ulrike Winkler, Ph.D.	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 25-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is subject to the transitional restriction provisions of Public Law 103-465, which became effective on June 8, 1995, because:

1. the application was filed on or before June 8, 1995, and has an effective U.S. filing date of June 8, 1992, or earlier;

2. a requirement for restriction was not made in the present or a parent application prior to April 8, 1995; and

3. the examiner was not prevented from making a requirement for restriction in the present or a parent application prior to April 8, 1995, due to actions by the applicant.

The transitional restriction provisions permit applicant to have more than one independent and distinct invention examined in the same application by paying a fee for each invention in excess of one.

Final rules concerning the transition restriction provisions were published in the *Federal Register* at 60 FR 20195 (April 25, 1995) and in the *Official Gazette* at 1174 O.G. 15 (May 2, 1995). The final rules at 37 CFR 1.17(s) include the fee amount required to be paid for each additional invention as set forth in the following requirement for restriction. See the current fee schedule for the proper amount of the fee.

Applicant must either: (1) elect the invention or inventions to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) for each independent and distinct invention in excess of one which applicant elects; or (2) file a petition under 37 CFR 1.129(b) traversing the requirement.

Applicant elected group I and elected to pay the additional fees for group II and III. Therefore, claims 1-23 and 25-41 are examined as they read on herpes virus.

Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection, which was necessitated by applicant's amendments to the claims.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not provide proper antecedent basis for the phrase "capable of raising neutralizing antibodies".

It is noted that the term "immunogenic composition" also does not have proper antecedent basis in the specification. However, the specification does have antecedent basis for the term "vaccine" which is known to be an immunogenic composition with a very narrow meaning in that it requires a prophylactic effect.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 32, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing neutralizing antibodies in mice when they are injected with truncated HSB gD glycoprotein, does not reasonably provide enablement for using any truncated glycoprotein as an immunogen to elicit neutralizing antibodies from any virus, fungal, microbial or parasitic organism that would be effective at protecting the animal from challenge by the pathogen. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to immunogenic compositions that are made up of membrane-free polypeptides. The claims would include truncated HIV glycoproteins. Most recombinant HIV-1 glycoproteins tested as vaccine candidates have been monomers and of gp120, even when these glycoproteins have been modified to assemble into dimers and tetramers the elicitation of neutralizing antibodies has been weak. This may be due to the fact that the biologically relevant envelope configuration on the cell surface is as a glycoprotein trimer (Yang et al., Journal of Virology 2001). Yang et al. show the production of soluble timers of HIV-1 in which the transmembrane (membrane binding domain) has been deleted and is effective for raising neutralizing antibodies. The reference indicates that there are definite structural requirement for the epitopes to obtain a good immune response. A single observation that encompasses the removal of a membrane binding domain to create a soluble polypeptide cannot be generalized to guarantee the production of an immune response "capable of raising neutralizing antibodies" that will be effective at preventing reinfection by the pathogen. The reference indicates that each antigen must be tested for its ability to raise a neutralizing immune response and that this cannot be predicated from the structure alone, should the structure even be known. Paul (Fundamental Immunology, Raven Press, New York, NY; 1993, 3rd Edition, pg. 251, column 1, lines 11-12) states that immunogenicity is limited by self-tolerance, and that the repertoire of potential antigenic sites in a given polypeptide is specific for the host organism. Paul also teaches (supra, pg. 249, column 2, lines 10-13) that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is

required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. The determination of an "epitope" or "antigenic determinant capable of raising neutralizing antibodies" is clearly a non-trivial enterprise, coupled with the lack of working examples for anything other than HSV gD in the specification, it would require undue experimentation for one of skill in the art to make and use the invention as claimed to cover all possible pathogenic immunogens.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-12, 14-19, 25-29, 32-41 are rejected under the judicially created doctrine of double patenting over claims 13, 19 and 20 of U. S. Patent No. 4,855,224 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter,

as follows: The claims of the instant application are drawn to an immunogenic composition that is devoid of a membrane-binding domain. The claims are interpreted to be product-by- process claims and therefore are interpreted as "a composition of matter" (which are products). Product-by- process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. M.P.E.P. Section 2113 states that:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

Looking to the specification for the description of the cell line producing the truncated diagnostic product. (see column 17, line 65 to column 18, line 4).

> The expression plasmid consisted of the pBR322 bacterial origin of replication and ampicillin resistance gene, a cDNA insert encoding the murine dihydrofolate reductase gene under the transcriptional control of the SV40 early promoter (53) and a HindIII-Hindf1 fragment which encodes the first 300 amino acids of gD under the transcriptional control of a second Sv40 early promoter. The HindIII site of this fragment lies 74 bp to the 5' side of the initiator methionine of the gD gene. The HindIII site of the SV-40 early region vector (36) lies 250 bp to the 3' side of the Goldberg-Hogness box of the SV40 promoter. The Hinf1 site (blunted with Klenow DNA polymerase and 4 deoxynucleotide triphosphates) is ligated to the Hpa1 site of the 3' nontranslated region of the hepatitis B virus surface antigen gene (36). This method is also useful for preparing a truncated HSV-2 gene.
>
> (see column 19, lines 37-44)
>
> The resulting vector was transfected (40) into a dhfr.sup.- CHO cell line (39), and a suitable clone gG10.2 selected which produced the truncated gD protein and secreted it into the surrounding medium. The protein was extracted from the medium and the cells were tested for immunogenic activity. FIG. 9 shows the results of immunoprecipita- tions of intra- and extra-cellular.sup.35 S-methionine-labelled extracts.

The patented claims are drawn to a diagnostic products, which have the same structure as the instantly claimed immunogenic composition. The product is a truncated membrane-free derivative of a polypeptide (comprising the first 300 amino acids), wherein the polypeptide is devoid of membrane binding domain and is free of membrane. The cell line expressing the product contains a plasmid with a selectable dhfr marker (see figure 8). Chemical compounds and their properties are inseparable, therefore, the limitation does not distinguish the instant invention over the prior art. See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). The instantly claimed immunogenic composition comprises the same structure as the patented diagnostic product. Therefore, the instant invention is obvious in view of the patented claims of U. S. Patent No. 4,855,224.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 10-41 are rejected under the judicially created doctrine of double patenting over claims 13, 19 and 20 of U. S. Patent No. 4,855,224 in view of Watson et al (Science 1992) and Dundarov et al. (Dev Biol Stand. 1982).

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: The claims of the instant application are drawn to an immunogenic composition that is devoid of a membrane-binding domain. The claims are interpreted to be product-by- process

claims and therefore are interpreted as "a composition of matter" (which are products). Product-by- process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps.

Looking to the specification for a detailed description of the cell line which is capable of producing the truncated diagnostic product (see column 17, line 65 to column 18, line 4; and column 19, lines 37-44), it is found that the patented claims drawn to the diagnostic product, have the same structure as the instantly claimed immunogenic composition. The diagnostic product is a truncated membrane-free derivative of a polypeptide (comprising the first 300 amino acids), wherein the polypeptide is devoid of membrane binding domain and is free of membrane. The cell line expressing the product contains a plasmid with a selectable dhfr marker (see figure 8). Chemical compounds and their properties are inseparable; therefore, the limitation does not distinguish instant invention over the prior art. See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). The patented claims do not teach HSV gB. However, the production of HSV gB immunogenic composition would be obvious over the patented claims in view of Watson et al., the reference teaches that HSV glycoproteins A-E are known and that antibodies to all of the glycoproteins are capable of neutralizing infection (see Watson column 1, 2nd paragraph). The teaching regarding glycoproteins A-E indicate that following the procedure provided in the patent would result in an immunogenic composition that would produce neutralizing antibodies to HSV gB. The patented claims also do not teach a polyvalent mixture of the immunogenic compositions, however, a combinations of the teachings in Watson et al. which indicates that neutralizing antibodies are made to all glycoproteins and the teaching in Dundarov et al. which use of polyvalent HSV vaccine for producing an immune resposne in a host. Therefore, the

instant invention drawn to an immunogenic composition comprising HSV gB, gC and gD and combinations thereof (polyvalent) and a cell line cable of producing the individual components of the immunogenic composition is obvious over the U. S. Patent No. 4,855,224 in view of Watson et al. and Dundarov et al.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 10, 11, 14-19 and 32-41 are rejected under the judicially created doctrine of double patenting over claims 1-10 of U. S. Patent No. 5,851,533 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: In the instant application the claims are drawn to an immunogenic composition comprising a truncated HSV gD which does not comprise a membrane anchor. The ability to elicit neutralizing antibodies is a feature attributed to the structure of the compound. Chemical compounds and their properties are inseparable, therefore, the limitation does not distinguish the instant invention over the prior art. See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The patented claims are drawn to a vaccine product, which has the same structure as the instantly claimed immunogenic composition. The product is a membrane-free polypeptide

having antigenic determinants. Looking to the specification for the description of the cell line producing the vaccine product, these cell lines contain a dhfr marker used for selection. The patented claims include a vaccine which comprises a membrane-free derivative of a polypeptide which does not contain a membrane binding domain. The instantly claimed immunogenic composition comprises the same structure as the patented vaccine. Therefore, the instant invention is drawn to an immunogenic composition comprising truncated (devoid of membrane binding domain) HSV gD and a cell line cable of producing the immunogenic composition is obvious in view of the U. S. Patent No. 5,851,533.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 1-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 1-5, 9, 13, 21, 22 and 25-27 of U. S. Patent No. 5,851,533 in view of Watson et al (Science 1992) and Dundarov et al. (Dev Biol Stand. 1982).

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: In the instant application the claims are drawn to an immunogenic composition comprising a truncated HSV gD which does not comprise a membrane anchor. The ability to elicit neutralizing antibodies is a feature attributed to the structure of the compound. Chemical compounds and their properties are inseparable, therefore, the limitation does not distinguish the

instant invention over the prior art. See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The patented claims are drawn to a vaccine product, which has the same structure as the instantly claimed immunogenic composition. The product is a membrane-free polypeptide having antigenic determinants. Looking to the specification for the description of the cell line producing the vaccine product, these cell lines contain a dhfr marker used for selection. The patented claims include a vaccine which comprises a membrane-free derivative of a polypeptide which does not contain a membrane binding domain. The instantly claimed immunogenic composition comprises the same structure as the patented vaccine. The patented claims do not teach HSV gB and gC. However, the production of HSV gB and gC immunogenic composition would be obvious over the teachings in the patent in view of Watson et al., the reference teaches that HSV glycoprotein A-E are known and that antibodies to all of the glycoproteins are capable of neutralizing infection (see Watson column 1, 2nd paragraph) indicating that following the procedure provided in the patent would result in an immunogenic composition that would produce neutralizing antibodies to HSV gB. The patented claims also do not teach a polyvalent mixture of the immunogenic compositions. However, Watson et al. indicates that neutralizing antibodies are made to all glycoproteins and Dundarov et al. teach the use of polyvalent HSV vaccine for producing an immune resposne in a host. Therefore, the instant invention drawn to an immunogenic composition comprising HSV gB, gC and gD and combinations thereof (polyvalent) and a cell line cable of producing the individual components of the immunogenic composition is obvious over the patented claims in view of Watson et al. and Dundarov et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

JEFFREY STUCKER
PRIMARY EXAMINER